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Short- and Long-term Mortality and Stroke Risk after Transcatheter Aortic Valve Implantation

Lars Jakobsen[a], MD, PhD; Christian J Terkelsen[a], MD, PhD, DMSc; Lars Søndergaard[b], MD, DMSc; Ole D Backer[b], MD, PhD; Jens Aarøe[c], MD, PhD; Henrik Nissen[d], MD, PhD; Søren P Johnsen[e], MD, PhD; Evald H Christiansen[a], MD, PhD.

[a]Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark.

[b]Department of Cardiology, Rigshospitalet, Copenhagen, Denmark.

[c]Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark

[d]Department of Cardiology, Odense University Hospital, Odense, Denmark

[e]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark

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Corresponding author:

Lars Jakobsen, MD, PhD

Department of Cardiology, Aarhus University Hospital

Palle Juul-Jensens Boulevard 99

8200 Aarhus N. Denmark

+45 22 80 76 44

larsj@dadlnet.dk

Running head: Mortality and stroke risk after TAVI

Abstract:

No published studies have compared the outcome after transcatheter aortic valve implantation (TAVI) with the outcome in the general population. Thus, it is unknown whether TAVI restores normal life expectancy and stroke risk. Furthermore, despite the increasing use of TAVI, only little is known about the temporal trends for TAVI regarding patient characteristics and outcomes. We identified all Danish patients treated with TAVI from 2006-2014 (n=1,631) and 9,737 general population controls matched by sex, age and comorbidity. The primary endpoint was a composite endpoint of all-cause mortality and stroke. During the first 90 days, the risk of the combined endpoint, the stroke risk and mortality were significantly higher among TAVI patients compared to controls (9.4%, 7.5% and 2.5% respectively in TAVI patients compared to 2.0%, 1.6% and 0.5% in controls). After 90 days, there were no differences (adjusted mortality rate ratio, stroke rate ratio and mortality or stroke rate ratio 0.92 (0.79-1.06), 1.32 (0.98-1.78), and 1.00 (0.90-1.10), respectively). During the study period, there were small changes in the characteristics of patients treated by TAVI; however, more patients were treated by transfemoral access; fewer needed blood transfusions, hospital stays were shorter, and the overall mortality rate decreased. In conclusion, 90 days post-TAVI, the stroke risk and mortality of the TAVI patients were comparable to the stroke risk and mortality of the general population. Over time, the patient risk profiles have remained largely unchanged; however outcomes have improved substantially including lower short- and long-term mortality.

Keywords: TAVI, mortality, stroke, temporal trends.

Aortic valve stenosis (AS) is the most common valvular heart disease in the Western World. If treated conservatively, patients with symptomatic severe AS have a poor prognosis[1]. During the last decade, transcatheter aortic valve implantation (TAVI) has become a widely accepted treatment modality which is now the treatment of choice in inoperable severe AS patients and as an alternative to surgery in patients with higher surgical risk[2, 3]. Lately, TAVI has also been shown to be a good alternative to surgical aortic valve implantation (SAVR) in intermediate-risk patients with outcomes after 2 years being comparable to SAVR[4-6]. A few studies have compared the outcome after SAVR with the general population[7, 8]. However, to our knowledge no published studies have compared the outcome after TAVI with the outcome in the general population using individual level data. Furthermore, despite the widespread use of TAVI as a well-established treatment modality, only little is known about the temporal trends for TAVI regarding patient characteristics and outcomes. The few existing studies indicate that TAVI is increasingly used in low-risk patients and that the outcome after TAVI is improving[9-11]. We therefore conducted a nationwide follow-up study comparing the mortality and stroke risk among all Danish patients treated with TAVI with the general population. Further, we evaluated the temporal trends in the patient and treatment characteristics, as well as short- and long term outcome, after TAVI.

METHODS

We conducted a national population-based historical follow-up study in Denmark with approximately 5.7 million inhabitants. The National Health Service provides tax-supported healthcare, guaranteeing unfettered access to medical care. All TAVI procedures are performed at four public hospitals in Denmark. The Danish Civil Registration System keeps records of sex, date of birth, and vital status. The records carry a 10-digit civil registration number assigned to every Danish citizen and used in all Danish registers, enabling unambiguous record linkage between them. The Web-PATS (Eastern Denmark) and the Western Denmark

Heart Registry (WDHR) collects detailed data related to patients and procedures for all interventions carried out in the 4 interventional centers performing TAVI in Denmark (Rigshospitalet, Copenhagen; Odense University Hospital; Aarhus University Hospital ; and Aalborg University Hospital). Reporting to the registries is mandatory and data quality is ensured by systematic validation procedures and random spot-checks of data after entry[12]. We identified all Danish patients treated with TAVI from 2006-2014 (n=1,631). Each patient was matched by sex and age with 40 individuals from the general population who were alive on the date of the associated patient's TAVI procedure. These controls were sampled using the Danish Civil Registration system. After computing the Charlson comorbidity index as a measure of comorbidity (described in next section), patients and controls were also matched by this index. The total number of controls was 9,737. The median number of controls for each TAVI patient was 8. It was not possible to identify at least one control for 106 TAVI patients (6.5% of all patients). We obtained data regarding baseline patient characteristics and all procedure-related data from the Web-PATS and the WDHR. The Danish National Patient Registry collects data for all hospitalisations at Danish hospitals, including dates of admission and discharge, and discharge diagnoses. Based on the last 10 years of hospitalization history for each patient and control, we computed the Charlson comorbidity index score[13], which was adapted for use with hospital discharge registry data[14]. We defined three levels of comorbidity: a score of 0 ("low"); a score of 1-2 ("moderate comorbidity"); and a score >2 ("high comorbidity"). The Danish Transfusion Database is a national registry monitoring the use of all blood components. We obtained information regarding the types and number of blood components administered from the day of the TAVI procedure and the following eight days. We obtained data regarding the use of cardiovascular drugs from the Danish Medicines Agency's Register of Medicinal Product Statistics, a national prescription registry that contains information on all redeemed prescriptions for reimbursable drugs dispensed from all pharmacies in Denmark (Data available until the end of 2015). The information includes type of drug and the date dispensed. We identified all prescriptions for aspirin, clopidogrel, statins, diuretics, angiotensin

converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, and selective and non-selective β-blockers filled from hospital discharge until the end of follow-up. In the comparison between patients treated with TAVI and the general population, the primary endpoint was a composite of all-cause mortality and stroke (ICD-10 I61, I63-64) after 90 days and 2 years. In the evaluation of the temporal trends, the primary endpoint was a composite of all-cause mortality and stroke at 30 days, one year, and two years. Data on stroke was obtained from the Danish National Patient Registry (data available until the end of 2015) and deaths were ascertained from The Danish Civil Registration System (data available until the end of 2016). The patients were censored at the time of death or followed until the end of 2016. Data regarding stroke; and thus, the composite endpoint were only available until the end of 2015. The mean follow-up time was 2 years. We used the Cox proportional hazards regression model to compute crude and adjusted hazard ratios (HR) and 95% confidence intervals (CI) for the endpoints. The hazards were not proportional throughout the follow-up period when comparing patients and general population controls; therefore, we estimated the HR within the periods during which the proportionality assumption held in these analyses (i.e., 0-90 days and >90 days-2 years); and we used a Cox model with delayed entry using age as the time scale. We adjusted for comorbidity as a continuous variable to reduce residual confounding. The general population controls served as the reference. The analyses were repeated after stratifying by treatment year of the TAVI patient. When evaluating the temporal trends, we compared baseline characteristics using the Student's t-test for continuous variables and the $\chi 2$-test for categorical variables. We used the Cox proportional hazards regression model to compute crude and adjusted HR and 95% CI for the endpoints. The patients were divided into three groups comparable in size according to the year of treatment (2006-2010, 2011-2012 and 2013-2014). The patients treated 2006-2010 served as the reference in all analyses and all tests of significance were two-tailed with $p<0.05$ considered statistically significant. Data regarding stroke and thus the combined endpoint after 2 years were only available for patients treated until the end of 2013. Analyses regarding these endpoints were based on patients treated

between 2006 and 2013. The number of patients with complete data for all variables was 672 (41%). However, for the individual variables, only a minor proportion of the patients had missing data (0.0%-10%). The exceptions were the Logistic EuroSCORE (37% missing) and atrial fibrillation (45% missing). We used multiple imputation to impute missing values for all variables. Besides all measured variables, we included the event indicator and the Nelson-Aalen estimator of the cumulative hazard to the survival time in the imputation model[15]. Analyses were conducted on 20 imputed datasets and the results combined using Rubin's rules[16]. Sex, age, and comorbidity were forced into all of the multivariable analyses. To optimize the precision of the risk estimation, we used the change-in-estimate method when selecting additional covariates to be included[17]. Covariates were selected based on a relative change of more than 10% in the estimated exposure effect. A family history of coronary artery disease, hypertension, peripheral artery disease, and site of implantation were in this way identified as possible confounding factors and included in the final multivariable model. The analyses were repeated after stratifying by sex and age (≤70 years, 70-80 years, >80 years). We analyzed data using Stata version 14.0 (StataCorp, College Station, TX, USA) software. Our study was approved by the Danish Data Protection Agency (journal number 2007-58-0010).

RESULTS

Table 1 and Figure 1 present mortality rates and cumulative mortality curves of the patients treated by TAVI and the sex-, age- and comorbidity matched general population controls. The rate of the composite endpoint, the mortality rate, and the stroke rate within 90 days were significantly higher among TAVI patients compared to controls. The adjusted mortality or stroke rate ratio, mortality rate ratio, and stroke rate ratio were significantly higher among patients compared to controls. After 90 days, there were no differences in the mortality rates or stroke rates compared with the general population. No substantial differences were observed when the analyses were stratified according treatment year of the TAVI patient (data not shown).

Table 2 shows the patient characteristics according to year of treatment. Compared to the patients treated from 2006-2010 more patients treated from 2011-2012 and from 2013-2014 had hypertension, chronic obstructive pulmonary disease, and atrial fibrillation whereas fewer were previous or active smokers, fewer had a family history of coronary artery disease, and fewer had a history of percutaneous coronary intervention or heart surgery. Fewer were treated with diuretics and aspirin prior to the TAVI procedure. Although not statistically significant, there was a trend towards higher preoperative ejection fraction, more peripheral artery disease and fewer patients with previous myocardial infarction over time. The treatment characteristics according to year of treatment are shown in table 3. Over time, more femoral procedures and fewer trans-apical procedures were performed. There were statistically significant differences in the valve type and valve size used in the three periods but no obvious trend over time was observed. Compared to the patients treated from 2006-2010 patients treated from 2011-2012 and from 2013-2014 had significantly shorter hospital stays. When comparing the use of medications after 1 year, fewer patients treated from 2013-2014 received aspirin compared to patients treated from 2006-2010 and 2011-2012. Over time, there was a significant decline in the proportion of patients treated with aspirin after 2 years. No differences in treatment with clopidogrel, β-blockers, angiotensin converting enzyme inhibitors/angiotensin II receptor blockers, statins, and diuretics after 1 year and 2 years were found (table 4). The cumulative risk of the combined endpoint after 1 year were 20.3%, 19.4%, and 14.9% among patients treated from 2006-2010, 2011-2012, and 2013-2014 respectively. The corresponding HR for patients treated from 2013-2014 compared to patients treated from 2006-2010 was 0.71 (0.53-0.95). Similar results were found after 30 days and although there was a clear trend towards similar results after 2 years, the differences were not statistically significant. The differences were mainly explained by differences in the cumulative mortality which reached statistical significance at all points in time, 2 year HR=0.75 (0.57-0.97). When comparing the cumulative risk of stroke, no differences were found at any point in time. Adjustment for differences in baseline characteristics did not change the results. When comparing

patients treated from 2006-2010 and patients treated from 2011-2012 no differences were found in any of the endpoints at any point in time. Table 5 shows the proportion of complications within 30 days. The proportion of patients receiving blood transfusions within 8 days after the TAVI-procedure was statistically significantly lower in the patients treated from 2011-2012 and 2013-2014 compared to patients treated from 2006-2010. There was no trend over time regarding the proportion of pacemaker implantations. However, significantly more patients treated between 2011 and 2012 had a pacemaker implanted compared to patients treated from 2006-2010 and from 2013-2014. We found no changes in the need for vascular surgery and treatment for haemopericardium. No substantial differences were observed when the analyses were stratified according to sex and age (data not shown).

DISCUSSION

Our study presents the patient characteristics, treatment characteristics, and outcomes in all the patients treated with TAVI in Denmark from the first implantation in 2006 and until 2014. The study has several important findings: (1) Beyond 90 days post-TAVI, the mortality and stroke rates of the patients were comparable to that of the general population; (2) there has been little change in the characteristics of patients treated by TAVI in Denmark from 2006 to 2014; (3) less invasive operative techniques have been widely adopted, i.e., more patients treated by transfemoral access; (4) outcomes have improved over time with a decrease in the need for blood transfusions, shorter hospital stays, and lower short- and longterm all-cause mortality. To the best of our knowledge, no published study has compared the prognosis after TAVI with the prognosis in the general population. Two previous studies have compared the quality of life and the long term survival between patients treated with SAVR and the general population. The studies showed comparable outcomes after SAVR compared to the general population[7, 8]. However, these studies did not have individual level data regarding the general population. Rather they compared their patients with expected values

regarding the quality of life and expected mortality using life time tables. In contrast to this, we were able to match our patients with a background population according to sex, age, and comorbidity. We found significantly higher mortality and stroke rates in the first 90 days after the TAVI-procedure. However, after the perioperative period, the mortality and stroke rates in the TAVI-patients were comparable to the mortality and stroke rates in the background population. The latter is positive and reassuring information which can be useful when informing patients about the prospects after TAVI. The limited changes over time in the characteristics of TAVI-patients in our study is in accordance with a previous study of all TAVI procedures performed in the United Kingdom from 2007-2012. The authors found a shift toward the treatment of patients with lower left ventricular ejection fraction. However, this was not associated with a change in the calculated Logistic EuroSCORE[10]. In contrast, two recent studies based on Israeli and French registries showed that over time TAVI is used in lower risk patients with less comorbidity. Both studies found a significant decrease in the mean logistic EuroSCORE / STS Risk Score during the study period[9, 11]. The adoption of less invasive access techniques in recent years is also in accordance with previous studies[9-11]. One study however, also found an increase in the use of the direct aortic approach, which we could not confirm in our study[10]. We found no changes in the need for vascular surgery. This corresponds with the findings of some[9, 11] but not all[10] previous studies. However, we obtained these data from the Danish National Patient Registry, and the validity of these data is known to be high[18]. We found a low incidence of vascular complications of only 1.7-2.4% compared to 2.6-5.5% in one study[10] and up to 15% in a second study[11]. This might indicate that there is a problem with validity of these data in our registries. However, our data regarding blood transfusions are very precise. These data show a statistically significant decrease in the need for blood transfusions during the perioperative period. One of the most obvious findings of our study was the marked decrease in the mean length of hospital stay from 10.2 days to 6.9 days in the earliest and the latest period respectively. Similar results have been found in all three previous studies[9-11]. We found lower cumulative risk of the combined endpoint after TAVI in patients treated

from 2013-2014 when comparing with earlier periods, although the changes were only significant after 1 year. This trend was mainly explained by a lower cumulative mortality over time. The changes in mortality were statistically significant after 30 days, 1 year and 2 years when comparing patients treated in the earliest and latest period. These results are also in accordance with the previous studies and the cumulative mortality in our study corresponds well to the previously found cumulative mortality[9-11]. However, in one of the studies, the differences in mortality were no longer statistically significant after adjustment for differences in baseline patient characteristics[9]. In the French study[11], they also found a decrease in the rate of stroke, which we did not find. The main strengths of our study are the relatively large number of patients, the long follow-up period, the prospective, population-based design, and the possibility of unambiguous individual-level linkage between public data sources, which provided detailed information on patient characteristics, treatments, and use of medications, and allowed complete follow-up, minimising the risk of selection bias. The Danish Civil Registration System and the Danish National Patient Registry made it possible to identify matched controls from the background population, which is unique. We used hospital discharge diagnoses, which may not always be accurate. However, the validity of the diagnoses included in this study were high (e.g., positive predictive values reported to be at least 80%)[18-21]. We did not take into account the percentage of patients who already had a pacemaker before the TAVI procedure. Thus, we have probably underestimated of the real rate of new pacemaker implantations. We controlled for a wide range of factors possibly affecting outcome; yet, due to the observational study design, we cannot exclude the possibility that confounding factors still influenced the results. In conclusion, after 90 days post-TAVI, the mortality and stroke rates of the TAVI patients were comparable to the mortality and the stroke rates of the general population. During the period from 2006-2014, the baseline patient risk profiles have remained largely unchanged. However, an increased use of transfemoral access has been adopted, fewer patients need blood transfusions peri-procedurally, the TAVI patients require a shorter hospital stays and the cumulative mortality has decreased over time.

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Figure legends

Figure 1: Cumulative incidence curves of the combined endpoint, mortality, and stroke in patients treated with transcatheter aortic valve implantation and sex, age, and comorbididy matched general population controls. Landmark analysis discriminating between events occurring before (A) and after 90 days of follow-up (B)

Table 1. Mortality rates and mortality rate ratios of the patients treated with transcatheter aortic valve implantation (TAVI) vs. age, sex and comorbidity matched controls from the general population. n/N (%)

		Mortality or stroke	Mortality	Stroke
0-90 days	TAVI	153/1631 (9.4 %)	123/1631 (7.5 %)	40/1631 (2.5 %)
	General population	197/9737 (2.0 %)	160/9737 (1.6 %)	46/9737 (0.5 %)
	Mortality / incidence rates*			
	TAVI vs. general population	408.2 (348.4-478.3) 82.5 (71.8-94.9)	322.9 (270.6-385.3) 67.3 (57.6-78.5)	101.4 (74.4-138.2) 19.2 (14.4-25.6)
	Adjusted mortality rate ratios† (95% confidence interval)	3.40 (2.75-4.21)	3.17 (2.48-4.06)	4.31 (2.77-6.71)
90 days - 2 years	TAVI	273/1478 (18.5 %)	232/1508 (15.3 %)	58/1478 (3.9 %)
	General population	1196/9540 (12.5 %)	1044/9577 (10.9 %)	227/9540 (2.4 %)
	Mortality / incidence rates*			
	TAVI vs. general population	116.6 (103.5-131.3) 76.3 (72.1-80.7)	94.9 (83.4-108.0) 65.8 (61.9-69.9)	21.2 (16.4-27.5) 13.5 (11.9-15.4)
	Adjusted mortality rate ratios† (95% confidence interval)	1.00 (0.90-1.10)	0.92 (0.79-1.06)	1.32 (0.98-1.78)

*per 1000 person years; †Mortality rate ratio adjusted for Charlson comorbidity score index.

Table 2. Baseline characteristics of patients treated with transcatheter aortic valve implantation according to treatment year. n/N (%)

Variable	2006-2010 (N=395)	2011-2012 (N=546)	2013-2014 (N=690)	Total (N=1631)
Men	194/395 (49.1 %)	286/546 (52.4 %)	359/690 (52.0 %)	839/1631 (51.4 %)
Age (years)				
<70	33/395 (8.4 %)	34/546 (6.2 %)	57/690 (8.3 %)	124/1631 (7.6 %)
70-80	120/395 (30.4 %)	220/546 (40.3 %)	229/690 (33.2 %)	569/1631 (34.9 %)
80-90	226/395 (57.2 %)	264/546 (48.4 %)	373/690 (54.1 %)	863/1631 (52.9 %)
>90	16/395 (4.1 %)	28/546 (5.1 %)	31/690 (4.5 %)	75/1631 (4.6 %)
Charlson comorbidity index				
0	102/395 (25.8 %)	142/546 (26.0 %)	170/690 (24.6 %)	414/1631 (25.4 %)
1-2	166/395 (42.0 %)	235/546 (43.0 %)	296/690 (42.9 %)	697/1631 (42.7 %)
≥3	127/395 (32.2 %)	169/546 (31.0 %)	224/690 (32.5 %)	520/1631 (31.9 %)
Body mass index (kg/m^2)				
<20	28/333 (8.4 %)	35/524 (6.7 %)	58/632 (6.7 %)	105/1489 (7.1 %)
20-25	129/333 (38.7 %)	175/524 (33.4 %)	333/632 (37.0 %)	538/1489 (36.1 %)
25-30	128/333 (38.4 %)	206/524 (39.3 %)	325/632 (33.7 %)	547/1489 (36.7 %)
>30	48/333 (14.4 %)	108/524 (20.6 %)	210/632 (22.6 %)	299/1489 (20.1 %)
Hypertension	238/381 (62.5 %)	361/533 (67.7 %)	488/671 (72.7 %)	1087/1585 (68.6 %)*
Dyslipidemia	192/383 (50.1 %)	285/538 (53.0 %)	379/678 (55.9 %)	856/1599 (53.5 %)
Diabetes mellitus	63/379 (16.6 %)	102/536 (19.0 %)	139/678 (20.5 %)	304/1593 (19.1 %)
Peripheral artery disease	64/393 (16.3 %)	97/545 (17.8 %)	135/686 (19.7 %)	296/1624 (18.2 %)
Cerebrovascular disease	40/393 (10.2 %)	67/545 (12.3 %)	90/689 (13.1 %)	197/1627 (12.1 %)
Chronic obstructive pulmonary disease	67/393 (17.1 %)	105/545 (19.3 %)	163/688 (23.7 %)	335/1626 (20.6 %)*
Atrial fibrillation	75/211 (35.6 %)	158/317 (49.8 %)	211/371 (56.9 %)	444/899 (49.4 %)*
Family history Coronary artery disease	177/361 (49.0 %)	149/483 (30.9 %)	214/616 (34.7 %)	540/1460 (37.0 %)*
Smoking, Active or previous	203/352 (57.7 %)	231/519 (44.5 %)	329/647 (50.9 %)	763/1518 (50.3 %)*
Previous myocardial infarction	69/386 (17.9 %)	81/531 (15.3 %)	96/673 (14.3 %)	246/1590 (15.5 %)
Previous percutaneous coronary intervention	101/391 (25.8 %)	126/530 (23.8 %)	132/676 (19.5 %)	359/1597 (22.5 %)*
Previous heart surgery	122/393 (31.0 %)	135/545 (24.8 %)	158/685 (23.1 %)	415/1623 (25.6 %)*
Left ventricular ejection fraction				
<30%	33/343 (9.6 %)	37/504 (7.3 %)	48/625 (7.7 %)	118/1472 (8.0 %)

30-45%	60/343 (17.5 %)	73/504 (14.5 %)	114/625 (18.2 %)	247/1472 (16.8 %)
>45%	250/343 (72.9 %)	394/504 (78.2 %)	463/625 (74.1 %)	1107/1472 (75.2 %)
Logistic EuroSCORE	15.8 (13.5-18.4 %)	15.5 (14.4-16.7 %)	15.0 (14.2-15.9 %)	15.2 (14.6-15.8 %)
Preoperative medications:				
Aspirin	298/355 (83.9 %)	400/496 (80.7 %)	468/657 (71.2 %)	1166/1508 (77.3 %)*
Clopidogrel	305/355 (85.9 %)	420/496 (84.7 %)	532/657 (81.0 %)	1257/1508 (83.4 %)
Beta-blocker	218/355 (61.4 %)	299/496 (60.3 %)	411/657 (62.6 %)	928/1508 (61.5 %)
ACE-I / AT2	158/355 (44.5 %)	242/496 (48.8 %)	314/657 (47.8 %)	714/1508 (47.4 %)
Statins	237/355 (66.8 %)	320/496 (64.5 %)	416/657 (63.3 %)	973/1508 (64.5 %)
Diuretics	297/355 (83.7 %)	398/496 (80.2 %)	505/657 (76.9 %)	1200/1508 (79.6 %)*

*p<0.05

ACE-I: Angiotensin converting enzyme inhibitor; AT2: Angiotensin 2 receptor blocker

Table 3. Treatment characteristics according to treatment year. n/N (%)

Variable	2006-2010 (N=395)	2011-2012 (N=546)	2013-2014 (N=690)	Total (N=1631)	
Site of implant					*
Femoral	227/393 (57.8 %)	378/546 (69.2 %)	503/688 (73.1 %)	1108/1627 (68.1 %)	
Apical	157/393 (39.9 %)	150/546 (27.5 %)	171/688 (24.9 %)	478/1627 (29.4 %)	
Subclavian	9/393 (2.3) %)	15/546 (2.7 %)	12/688 (1.7 %)	36/1627 (2.2 %)	
DirectAortic	0	3/546 (0.6 %)	2/688 (0.3 %)	5/1627 (0.3 %)	
Valve type					*
Core valve	197/381 (51.7 %)	294/537 (54.7 %)	278/681 (40.8 %)	769/1599 (48.1 %)	
Portico	0	0	18/681 (2.6 %)	18/1599 (1.1 %)	
Sapien (Cribier)	74/381 (19.4 %)	44/537 (8.2 %)	18/681 (2.6 %)	136/1599 (8.5 %)	
Sapien XT	110/381 (28.9 %)	199/537 (37.1 %)	232/681 (34.1 %)	541/1599 (33.9 %)	
Sapien 3	0	0	135/681 (19.8 %)	135/1599 (8.4 %)	
Valve size (mm)					*
≤23	50/288 (17.4 %)	56/508 (11.0 %)	89/659 (13.5 %)	195/1455 (13.4 %)	
24-26	146/288 (50.7 %)	223/508 (43.9 %)	277/659 (42.0 %)	646/1455 (44.4 %)	
≥27	92/288 (31.9 %)	229/508 (45.1 %)	293/659 (44.5 %)	614/1455 (42.2 %)	
Peri-procedural blood transfusion	167/395 (42.3 %)	163/546 (29.9 %)	161/690 (23.3 %)	491/1631 (30.1 %)*	
Length of stay (days)	10.2 (9.1-11.3)	8.1 (7.6-8.6)	6.9 (6.5-7.3)	8.1 (7.7-8.5)*	
Discharge day after Transcatheter aortic valve implantation					
3.	23/380 (6.1 %)	45/537 (8.4 %)	106/687 (15.4 %)	174/1604 (10.9 %)*	
4.	40/380 (10.5 %)	115/537 (21.4 %)	230/687 (33.5 %)	385/1604 (24.0 %)*	
5.	62/380 (16.3 %)	171/537 (31.8 %)	319/687 (46.4 %)	552/1604 (34.4 %)*	

*p<0.05

Table 4. Medical treatment characteristics according to treatment year. n/N (%)

Variable	2006-2010 (N=395)	2011-2012 (N=546)	2013-2014 (N=690)	Total (N=1631†)
Preoperative medications:				
• Aspirin	298/355 (83.9 %)	400/496 (80.7 %)	468/657 (71.2 %)	1166/1508 (77.3 %)*
• Clopidogrel	305/355 (85.9 %)	420/496 (84.7 %)	532/657 (81.0 %)	1257/1508 (83.4 %)
• Beta-blocker	218/355 (61.4 %)	299/496 (60.3 %)	411/657 (62.6 %)	928/1508 (61.5 %)
• ACE-I / AT2	158/355 (44.5 %)	242/496 (48.8 %)	314/657 (47.8 %)	714/1508 (47.4 %)
• Statins	237/355 (66.8 %)	320/496 (64.5 %)	416/657 (63.3 %)	973/1508 (64.5 %)
• Diuretics	297/355 (83.7 %)	398/496 (80.2 %)	505/657 (76.9 %)	1200/1508 (79.6 %)*
Medical treatment 1 year				
• Aspirin	245/319 (76.8 %)	323/448 (72.1 %)	333/598 (55.7 %)	901/1365 (66.0 %)*
• Clopidogrel	104/319 (32.6 %)	125/448 (27.9 %)	187/598 (31.3 %)	416/1365 (30.5 %)
• Beta-blocker	178/319 (55.8 %)	245/448 (54.7 %)	337/598 (56.4 %)	760/1365 (55.7 %)
• ACE-I / AT2	148/319 (46.4 %)	205/448 (45.8 %)	269/598 (45.0 %)	622/1365 (45.6 %)
• Statins	201/319 (63.0 %)	263/448 (58.7 %)	374/598 (62.5 %)	838/1365 (61.4 %)
• Diuretics	244/319 (76.5 %)	317/448 (70.8 %)	409/598 (68.4 %)	970/1365 (71.1 %)
Medical treatment 2 year				
• Aspirin	223/288 (77.4 %)	253/401 (63.1 %)	129/265 (48.7 %)	605/954 (63.4 %)*
• Clopidogrel	35/288 (12.2 %)	75/401 (18.7 %)	41/265 (15.5 %)	151/954 (15.8 %)
• Beta-blocker	154/288 (53.5 %)	212/401 (52.9 %)	158/265 (59.6 %)	524/954 (54.9 %)
• ACE-I / AT2	143/288 (49.7 %)	187/401 (46.6 %)	117/553 (44.2 %)	447/954 (46.9 %)
• Statins	172/288 (59.7 %)	236/401 (58.9 %)	153/553 (57.7 %)	561/954 (58.8 %)
• Diuretics	207/288 (71.9 %)	278/401 (69.3 %)	172/553 (52.4 %)	657/954 (68.9 %)

*p<0.05

†data regarding medical treatment after 2 years only available for patients treated until the end of 2013. Data regarding these endpoints based on patients treated in 2013 only (n=330)

ACE-I: Angiotensin converting enzyme inhibitor; AT2: Angiotensin 2 receptor blocker

Table 5. Complications in patients treated with transcatheter aortic valve implantation according to year of treatment. n(%)

Complication	2006-2010 (N=395)	2011-2012 (N=546)	2013-2014 (N=690)
Bloodtransfusion within 7 days	167 (42.3 %)	163 (29.9 %)	161 (23.3 %)*
Pacemaker implantation	61 (15.4 %)	104 (19.1 %)	95 (13.8 %)*

within 30 days			
Vascular surgery, femoral artery or infrarenal aorta within 30 days	11 (2.8 %)	9 (1.7 %)	11 (1.6 %)
Treated for haemopericardium within 30 days	3 (0.8 %)	1 (0.2 %)	1 (0.1 %)
Surgery on thoracic aorta within 30 days	0	0	0

*p<0.05

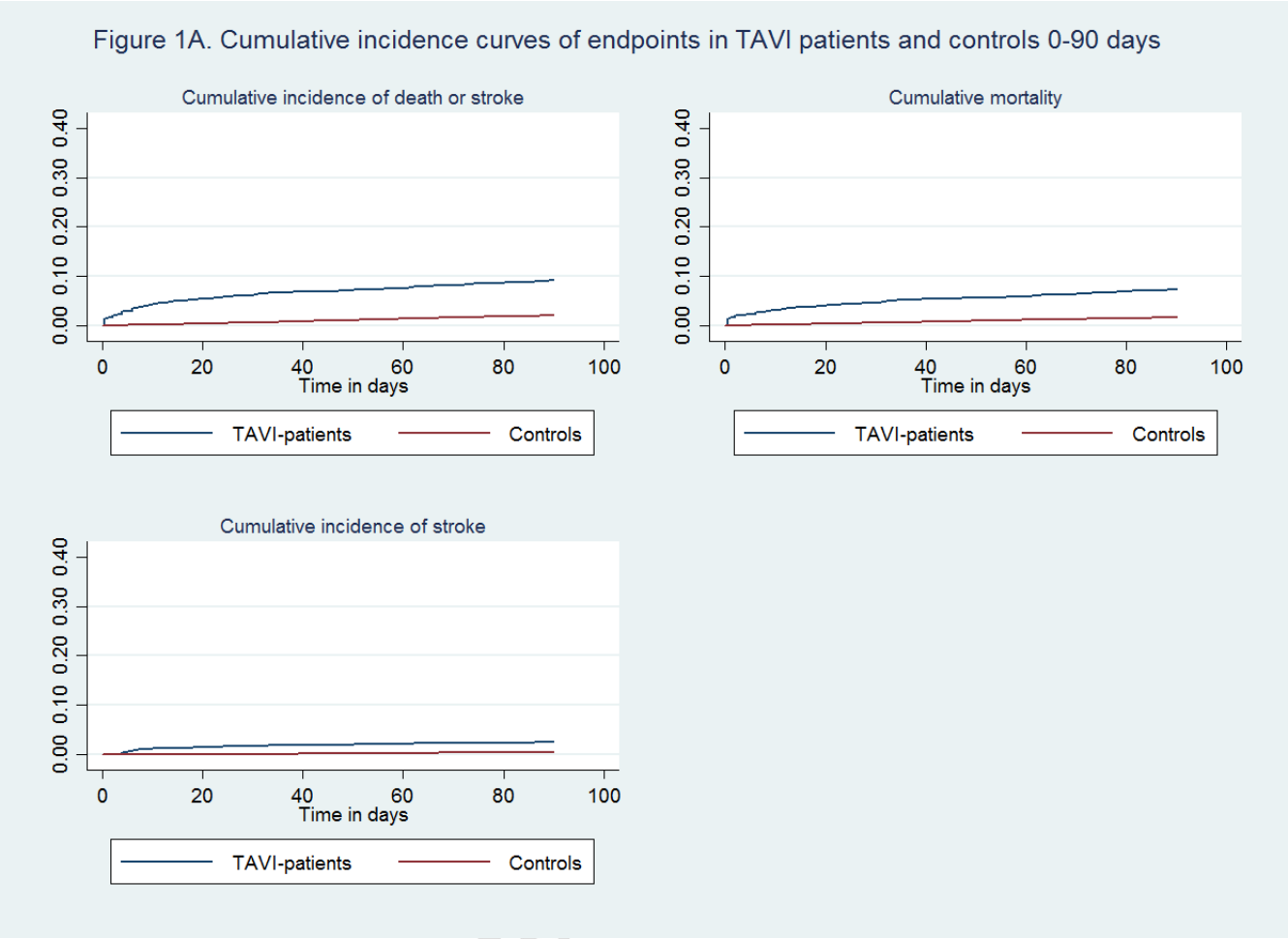

Figure 1A_bestsetConverted.png

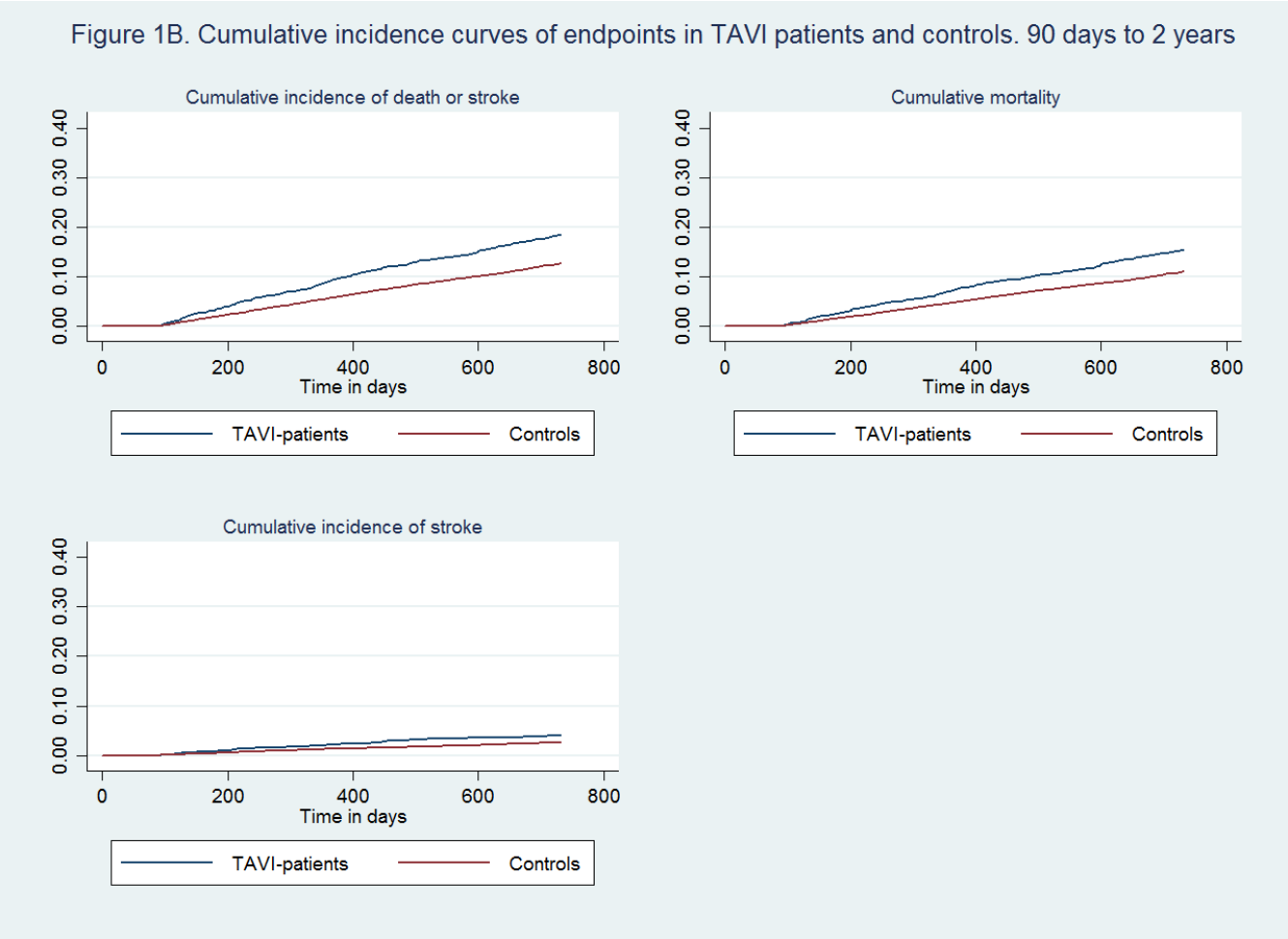

Figure 1B_bestsetConverted.png